The Role of Microbes in Chronic Sinusitis

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Disclosures

- Co-author patent application regarding “Sinusitis diagnostics and treatments”
- Consultant, Bioinspire
Outline

- Background on microbes and human health
- Interaction between microbes and host organisms
- Role of microbes in Chronic Rhinosinusitis

Microbes in Human Health

- Since the 1800’s, medicine has been dominated by a pathogen-centric approach to the study of microorganisms
- Culture-dependent bacterial identification
  - Koch’s postulates
Microbes in Human Health

- “War” on microbes with antibiotics
  - Scorched-earth approach

- Antibiotic treatment is a major medical advance, but ...
- Collateral Damage with antimicrobials?
- Can antibiotic overuse result in individual disease susceptibility, not just problems of community resistance?
Microbes in Human Health

- Advances in microbial understanding
  - Culture-independent microbial identification
    - 16s rRNA identification
  - NIH Human Microbiome Project 2007
    - $17 million
    - Concluded in 2012
  - Microbiome: the totality of microbes within a given environment

- Evolving understanding of the role of microbes
  - Microbes live in communities; they both influence and are influenced by their environment
  - Microbial behavior is contextual
  - Microbes compete, cooperate, and influence one-another and their living and non-living host environments
Microbes in Human Health

- In humans, the ratio of microbes to human cells is estimated to be greater than 10:1
- Diversity of genetic information within microbiome dwarfs that of its human hosts
- Symbiotic Co-evolution

Symbiotic Coevolution

- Euprymna Scolopes
  - Hawaiian Bobtail Squid
- Vibrio Fischeri
  - Bioluminescent bacteria provides camouflage

Nyholm and McFall-Ngai. Nature Reviews Microbiology, 2004
Co-evolution in Humans?

- Human breast milk
  - Sole nutrient source for infants
  - Majority of oligosaccharides are not digestible for human infants


Co-evolution in Humans?

- Human breast milk
  - Oligosaccharides nourish Bifidobacterium
  - Impacts interaction with human gut epithelium

The Microbiome and Human Health

- Early focus on GI tract and “Colonization Resistance”
  - Enteropathogens proliferate in the setting of a depleted microbiota
  - Efficacy of the fecal transplant

Kelly CP, NEJM 2013 368:474-475

The Microbiome and Human Health

- Microbial interactions with the immune system
  - Hygiene Hypothesis
  - Early antibiotic exposure increases incidence of IBD, Asthma
  - C-section birth increases risk of asthma

The Microbiome and Human Health

- Inflammatory Bowel Disease
  - Animal models of colitis demonstrate increased inflammation in the setting of microbial depletion
  - Cause or effect?
  - Diminished microbial production of short-chain fatty acids results in increased tissue infiltration of neutrophils

“(In animal models of IBD) both the innate and the adaptive limbs of the mucosal immune response are stimulated or restrained by the effects of intestinal microbes.”

Chronic Rhinosinusitis

- Inflammatory disorder
- Role of bacteria?
  - Infection
  - Impact mucosal immune function

Miocrobiome and the Sinuses

- Hypothesis: Dysbiosis of the paranasal sinus microbiome provides a setting for chronic inflammation which manifests as chronic sinusitis
Evaluating the Microbiome

- Are there microbes in the sinuses of healthy patients?
- Culture independent methods of bacterial identification
  - 16s rRNA PhyloChip
  - High throughput sequencing of 16s Gene

Culture-Independent Bacterial Identification

- Allows for detection and quantification of low-abundance species
- Provides identification of bacteria in the Biofilm state
  - Viable but non-culturable
- Microbial ecology – study of microbial communities, not just individual organisms
Initial Study

- Comparison of the sinus microbial community in patients with chronic sinusitis vs. control
  - Control sinuses not sterile
  - No difference in total bacterial count between CRS and control patients

Roediger et al AJR 2010

Microbial Diversity in CRS

Abreu et al STM 2012
Cluster Analysis of Microbial Communities

Phylogenetic Tree of Bacteria Identified
Murine Model of Sinusitis

- Cause vs. Effect?
- Evaluate pathogenic potential of C. Tuberculostearicum
- Investigate contribution of native microbiome to development of sinus disease

4 groups of mice
- C. Tuberculostearicum inoculation
- Antibiotic (Amox/Clav) treated
- Antibiotic treatment followed by C. Tuberculostearicum inoculation
- Control

Evaluate sinus histology
Murine Model of Sinusitis

A

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![Images of histological sections](image)

100 μm

Murine Model of Sinusitis

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Murine Model of Sinusitis

- Role of Probiotic?
  - Antibiotic treated followed by L. Sakei inoculation
  - Antibiotic treated followed by co-instillation of L. Sakei and C. Tuberculostearicum
  - Positive and negative controls
- Evaluate sinus histology

Probiotic Effect in Murine Model
Probiotic Effect in Murine Model

Antibiotics Impact Microbiome Composition

“Every course of antibiotics may represent another roll of the dice, potentially allowing displacement of a mutualist with a strain that may or may not provide the same benefit”

Summary

- CRS is characterized by a loss of microbial diversity in the paranasal sinuses
- C. Tuberculostearicum identified as a novel pathobiont of the sinuses
Summary

- Perturbation of the native microbial community provides the setting for pathogenic bacterial overgrowth
- Probiotics may play a role in the prevention and/or treatment of CRS

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